PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Form PCT/IPEA/416
RJW/6211999		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB2004/002101	14.05.2004	15.05.2003

International Patent Classification (IPC) or national classification and IPC
C07C323/62, C07D213/70, C07D333/38, A61K31/10, A61K31/44, A61K31/4436, A61K31/381, A61P35/00

Applicant
CHROMA THERAPEUTICS LIMITED et al.

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 9 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
07.03.2005	12.09.2005
Name and mailing address of the international preliminary examining authority:	Authorized Officer
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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/002101

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-62 as originally filed

   Claims, Numbers

   1-50 received on 07.03.2005 with letter of 03.03.2005

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 33

because:

☒ the said international application, or the said claims Nos. 33 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-50
	No:	Claims	
Inventive step (IS)	Yes:	Claims	32-50
	No:	Claims	1-31
Industrial applicability (IA)	Yes:	Claims	1-32,34-50
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item III.

1. Claim 33 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

   For the assessment of the present claim 33 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item V.

D1: US-A-4 898 870 (NARUTOMI YUJI ET AL) 6 February 1990 (1990-02-06)
D2: WO 99/35128 A (UNIV MARYLAND AT BALTIMORE COU) 15 July 1999 (1999-07-15)
D3: DATABASE BEILSTEIN BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; XP002297491 retrieved from XFIRE accession no. BRN 5300594, 5139287, 5137246
D4: DATABASE BEILSTEIN BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; XP002297492 retrieved from XFIRE accession no. BRN 5133758
D5: DATABASE BEILSTEIN BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; XP002297493 retrieved from XFIRE accession no. BRN 4489731
D6: DATABASE BEILSTEIN BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; XP002298184 accession no. BRN 2047546
D7: DATABASE BEILSTEIN BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY,

FRANKFURT-MAIN, DE; XP002298185 accession no. BRN 7543266

D8: DATABASE BEILSTEIN BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; XP002298186 accession no. BRN 1994106

D9: DATABASE BEILSTEIN BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; XP002298187 accession no. BRN 3593422

D10: DATABASE BEILSTEIN BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; XP002298188 accession no. BRN 246624

D11: DATABASE BEILSTEIN BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; XP002298189 accession no. BRN 2334448

1. After restriction of the scope of present claims 1 to 30 by restriction of the definition of the variable L^1 novelty of present claims 1 to 31 as well as 32 to 50 is given: none of the available prior art documents D1 to D11 discloses a first medical use or a pharmaceutical composition relating to compounds according to formula I or formula Ib.

   The subject matter of present claims 1 to 31 is thus novel over said prior art (PCT Article 33.2).

2. The use in any method of therapy of the compounds of present claims 1 to 30 as well as any pharmaceutical compositions containing these compounds have to be regarded as being mere obvious alternatives of the uses and pharmaceutical compositions of the compounds disclosed in D6 to D11.
   Having regard to the close structural relationship of the compounds of D6 to D11 with the compounds of present formulae I and Ib it is considered that the skilled person does not need any inventive afford to modify the prior art compounds in a way that they fall within the scope of present formulae I and Ib.

   The subject matter of present claims 1 to 31 is thus not based on an inventive step over said prior art (PCT Article 33.3).

3. None of the documents D3 to D11 disclose the use of the compounds as inhibitors of glyoxalyse I.
The subject matter of present claim 32 is thus novel as well as inventive over said prior art (PCT Article 33.2 and 33.3).

4. D1 and in particular D2 can be regarded as the closest prior art document. Both documents disclose compounds which are inhibitors of glyoxalase I and which are due to this activity possible agents in the treatment of cancer.

   The underlying problem is seen in the provision of further inhibitors of glyoxalase I whereby the novel inhibitors have a non-peptidic structure.

5. The claimed compounds (claim 34) differ structurally from the compounds of D1 since D1 discloses quinone-derivatives; such a structure is not included within the presently claimed compounds and additionally the compounds of D1 have no thio-ether-group. The compounds of D2 are structurally also remote from the claimed ones; one difference represents the sulfone- or sulfoxide-group in D2 which is not present in the presently claimed compounds.
The subject matter of present claims 34 to 50 is thus novel over said prior art (PCT Article 33.2).

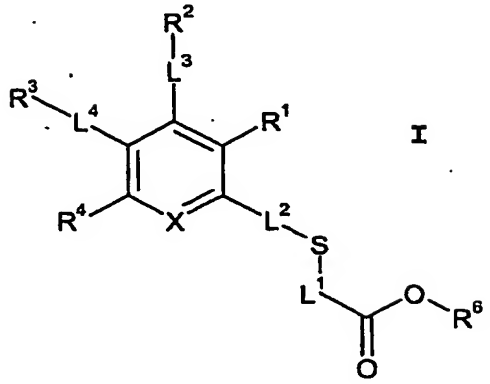
   As could be demonstrated by the performed examples, the claimed compounds are considered to solve the underlying problem.
Due to the structural difference between the prior art and the compounds of claim 34 an inventive step can be acknowledged since it was not obvious to the skilled person that starting from either D1 or D2 the compounds of claim 34 would show the wanted activity.
The subject matter of present claims 34 to 50 is considered to be based on an inventive step over said prior art (PCT Article 33.3).

6. Industrial applicability is given for present claims 1 to 32 and 34 to 50 (PCT Article 33.4).

7. The description is not in line with the claims on file (PCT Article 6).

Claims

1. A compound of formula I:



I

wherein

X is N or CH;

R^1 is H, cyano, halo, hydroxy, hydroxamic acid, sulfhydryl or $-NH_2$; or C_{1-4} alkyl optionally substituted by cyano, halo, hydroxy, hydroxamic acid, sulfhydryl or $-NH_2$; or $-OR$, $-NHR$, $-NR_2$ or $-SR$ wherein R is C_{1-4} alkyl optionally substituted by cyano, halo, hydroxy, hydroxamic acid, sulfhydryl or $-NH_2$;

R^2 is H, CF_3; or optionally substituted C_{5-6} aryl, C_{3-7} cycloalkyl, C_{5-7} heterocyclyl or together with R^3 an optionally substituted C_{3-4} alkylene group wherein L^3 and L^4 are single bonds thus forming a C_{5-6} ring fused with the aromatic ring to which L^3 and L^4 are attached;

R^3 is H; or optionally substituted C_{5-6} aryl, C_{3-7} cycloalkyl, C_{5-7} heterocyclyl or together with R^2 an optionally substituted C_{3-4} alkylene group wherein L^3 and L^4 are single bonds thus forming a C_{5-6} ring fused with the aromatic ring to which L^3 and L^4 are attached;

R^4 is H; or optionally substituted C_{5-6} aryl or C_{5-7} heterocyclyl;

R^6 is selected from H or optionally substituted C_{1-7} alkyl, C_{5-6} aryl and C_{1-4} alkylene-C_{5-6} aryl;

L^1 is optionally substituted C_{5-6} arylene, C_{1-4} alkylene-

C_{5-6} arylene or $-L^5N(R^5)L^6-$, or C_{1-4} alkylene substituted by either C_{1-7} alkyl or C_{5-7} aryl, wherein L^5 and L^6 are independently selected from optionally substituted C_{1-4} alkylene and C_{5-6} arylene, and R^5 is H or C_{1-4} alkyl; and further wherein L^1 may be unsubstituted C_{1-4} alkylene when X is N;

L^2 is a single bond; or optionally substituted C_{1-4} alkylene or $-L^7C(=O)L^8-$, wherein L^7 and L^8 are independently selected from optionally substituted C_{1-4} alkylene and a single bond; and

L^3 and L^4 are independently selected from a single bond, optionally substituted C_{1-4} alkylene, $-L^9YN(OH)C(=O)L^{10}-$ and $-L^9C(=O)N(OH)YL^{10}-$, wherein L^9 and L^{10} are independently selected from optionally substituted C_{1-4} alkylene, C_{5-6} arylene, C_{1-4} alkylene-C_{5-6} arylene and a single bond, wherein Y is NH or a single bond;

or a pharmaceutically acceptable salt thereof for use in a method of therapy.

2. A compound according to claim 1 wherein R^1 is chosen from the group consisting of H and cyano.

3. A compound according to any one of the preceding claims wherein R^6 is H or C_{1-7} alkyl.

4. A compound according to any one of the preceding claims wherein L^1 is chosen from the group consisting of phenylene, -CH(Ph)-, $-CH_2$-phenylene- and $-CH_2C(=O)NH$-phenylene-.

5. A compound according to any one of the preceding claims wherein L^2 is a single bond or $-C(=O)CH_2-$.

6. A compound according to any one of the preceding claims wherein L^3 is chosen from the group consisting of a single bond, $-L^9YN(OH)C(=O)L^{10}-$ and $-L^9C(=O)N(OH)YL^{10}-$, wherein L^9 and L^{10} are independently selected from optionally substituted C_{1-4} alkylene, C_{5-6} arylene, C_{1-4} alkylene-C_{5-6} arylene and a single bond, and wherein Y is NH or a single bond.

7. A compound according to claim 6 wherein L^3 is a single bond.

8. A compound according to any one of the preceding claims wherein L^4 is chosen from the group consisting of a single bond, $-L^9YN(OH)C(=O)L^{10}-$ and $-L^9C(=O)N(OH)YL^{10}-$, wherein L^9 and L^{10} are independently selected from optionally substituted C_{1-4} alkylene, C_{5-6} arylene, C_{1-4} alkylene-C_{5-6} arylene and a single bond, and wherein Y is NH or a single bond.

9. A compound according to claim 8 wherein L^4 is selected from the group consisting of $-CH_2N(OH)C(=O)-$, -phenylene-$CH_2N(OH)C(=O)-$, -phenylene-$NHN(OH)C(=O)-$ and $-CH_2C(=O)N(OH)-$.

10. A compound according to any one of the preceding claims wherein X is CH.

11. A compound according to claim 10 wherein one of R^1, R^2 and R^4 are H.

12. A compound according to claim 10 wherein two of R^1, R^2 and R^4 are H.

13. A compound according to claim 10 wherein R^1, R^2 and R^4 are all H.

14. A compound according to claim 10 wherein one of R^2 and R^3 is optionally substituted C_{5-6} aryl, C_{3-7} cycloalkyl or C_{5-7} heterocyclyl.

15. A compound according to claim 14 wherein R^3 is optionally substituted C_{5-6} aryl, C_{3-7} cycloalkyl or C_{5-7} heterocyclyl.

16. A compound according to claim 14 wherein R^3 is optionally substituted phenyl or C_{3-7} cycloalkyl.

17. A compound according to claim 14 wherein R^3 is phenyl or cyclopentyl.

18. A compound according to claim 10 wherein L^1 is phenylene or -CH(Ph)-.

19. A compound according to claim 10 wherein one of L^3 and L^4 is a single bond.

20. A compound according to claim 19 wherein L^3 is a single bond.

21. A compound according to any one of claims 1 to 9 wherein X is N.

22. A compound according to claim 21 wherein R^4 is selected from optionally substituted C_{5-6} aryl and C_{5-7} heterocyclyl.

23. A compound according to claim 21 or 22 wherein R^1 is cyano or hydroxamic acid.

24. A compound according to claim 21 or 22 wherein R^2 is selected from the group consisting of optionally substituted C_{5-6} aryl, C_{5-7} heterocyclyl, CF_3 and, together with R^3, an optionally substituted butylene group wherein L^3 and L^4 are single bonds thus forming a C_6 ring fused with the aromatic ring to which L^3 and L^4 are attached.

25. A compound according to claim 24 wherein R^2 is selected from optionally substituted C_{5-6} aryl or C_{5-7} heterocyclyl.

26. A compound according to claim 24 wherein R^2 is selected from optionally substituted phenyl or thiophenyl.

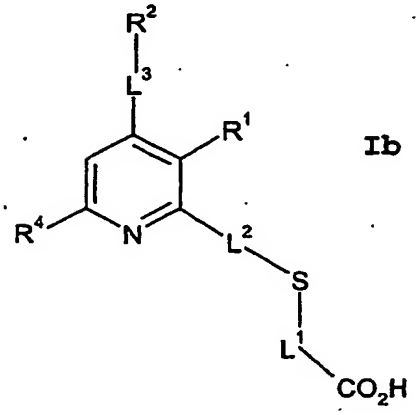
27. A compound according to claim 24 wherein R^2 is selected from the group consisting of thiophenyl, phenyl, *p*-chlorophenyl, *p*-methoxyphenyl, *o*-methoxyphenyl and *p*-fluorophenyl.

28. A compound according to any one of claims 24 to 26 wherein R^2 is a monosubstituted phenyl group with the substituent group being in the *para* position.

29. A compound according to any one of claims 21 to 28 wherein R^3 is H or, together with R^2, an optionally substituted butylene group wherein L^3 and L^4 are single bonds thus forming a C_6 ring fused with the aromatic ring to which L^3 and L^4 are attached.

30. A compound according to claim 29 wherein R^3 is H and

L^4 is a single bond such that the compound is of formula **Ib**:



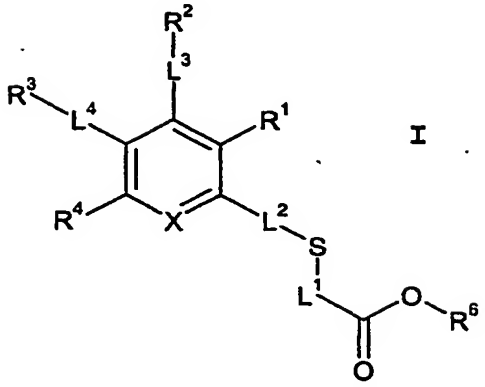
Ib

31. A pharmaceutical composition comprising a compound according to any one of the preceding claims or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent.

32. Use of a compound according to any one of claims 1 to 30 or a pharmaceutically acceptable salt thereof in the preparation of a medicament for the treatment of a condition alleviated by inhibition of glyoxalase I.

33. A method of treating a condition which can be alleviated by inhibition of glyoxalase I, which method comprises administering to a patient in need of treatment an effective amount of a compound according to any one of claims 1 to 30, or a pharmaceutically acceptable salt thereof.

34. A compound of formula **I**:



I

or a salt, solvate or chemically protected form thereof wherein

X is N or CH;

R^1 is H, cyano, halo, hydroxy, hydroxamic acid, sulfhydryl or $-NH_2$; or C_{1-4} alkyl optionally substituted by cyano, halo, hydroxy, hydroxamic acid, sulfhydryl or $-NH_2$; or $-OR$, $-NHR$, $-NR_2$ or $-SR$ wherein R is C_{1-4} alkyl optionally substituted by cyano, halo, hydroxy, hydroxamic acid, sulfhydryl or $-NH_2$;

R^2 is H, CF_3; or optionally substituted C_{5-6} aryl, C_{3-7} cycloalkyl, C_{5-7} heterocyclyl or together with R^3 an optionally substituted C_{3-4} alkylene group wherein L^3 and L^4 are single bonds thus forming a C_{5-6} ring fused with the aromatic ring to which L^3 and L^4 are attached;

R^3 is H; or optionally substituted C_{5-6} aryl, C_{3-7} cycloalkyl, C_{5-7} heterocyclyl or together with R^2 an optionally substituted C_{3-4} alkylene group wherein L^3 and L^4 are single bonds thus forming a C_{5-6} ring fused with the aromatic ring to which L^3 and L^4 are attached;

R^4 is H; or optionally substituted C_{5-6} aryl or C_{5-7} heterocyclyl;

R^6 is selected from H or optionally substituted C_{1-7} alkyl, C_{5-6} aryl and C_{1-4} alkylene-C_{5-6} aryl;

L^1 is optionally substituted C_{1-4} alkylene, C_{5-6} arylene, C_{1-4} alkylene-C_{5-6} arylene or $-L^5N(R^5)L^6-$, wherein L^5 and L^6

are independently selected from optionally substituted C_{1-4} alkylene and C_{5-6} arylene, and R^5 is H or C_{1-4} alkyl;

L^2 is a single bond; or optionally substituted C_{1-4} alkylene or $-L^7C(=O)L^8-$, wherein L^7 and L^8 are independently selected from optionally substituted C_{1-4} alkylene and a single bond; and

L^3 and L^4 are independently selected from a single bond, optionally substituted C_{1-4} alkylene, $-L^9YN(OH)C(=O)L^{10}-$ and $-L^9C(=O)N(OH)YL^{10}-$, wherein L^9 and L^{10} are independently selected from optionally substituted C_{1-4} alkylene, C_{5-6} arylene, C_{1-4} alkylene-C_{5-6} arylene and a single bond, wherein Y is NH or a single bond; and

wherein the compound contains at least one $-C(=O)N(OH)-$ group.

35. A compound according to claim 34 wherein at least one of R^1, L^3 or L^4 comprises a $-C(=O)N(OH)-$ group.

36. A compound according to claim 34 wherein L^4 comprises a $-C(=O)N(OH)-$ group.

37. A compound according to any one of claims 34 to 36 wherein L^4 is a $L^9-C(=O)N(OH)-$ group.

38. A compound according to claim 37 wherein L^9 is selected from C_{1-4} alkylene and C_{5-6} arylene.

39. A compound according to claim 37 wherein L^9 is methylene or phenylene.

40. A compound according to any one of claims 34 to 39 wherein X is CH.

41. A compound according to any one of claims 34 to 40 wherein at least one of R^1, R^2 and R^4 is H.

42. A compound according to any one of claims 34 to 40 wherein at least two of R^1, R^2 and R^4 are H.

43. A compound according to any one of claims 34 to 40 wherein all of R^1, R^2 and R^4 are H.

44. A compound according to any one of claims 34 to 43 wherein R^3 is optionally substituted C_{5-6} aryl.

45. A compound according to claim 44 wherein R^3 is phenyl.

46. A compound according to any one of claims 34 to 45 wherein R^6 is H or C_{1-7} alkyl.

47. A compound according to claim 46 wherein R^6 is H or C_{1-3} alkyl.

48. A compound according to any one of claims 34 to 47 wherein L^1 is phenylene, -CH(Ph)-, $-CH_2$-phenylene- or $-CH_2C(=O)NH$-phenylene-.

49. A compound according to any one of claims 34 to 48 wherein L^2 is a single bond or $-C(=O)CH_2-$.

50. A compound according to any one of claims 34 to 49 wherein L^3 is a single bond.